

Original Article

The Correlation between Methadone Dosage and Comorbid Psychiatric Disorders in Patients on Methadone Maintenance Treatment

Nooshin Parvaresh MD¹, Arman Masoudi MD², Shiva Majidi-Tabrizi MA³,
Shahrzad Mazhari MD⁴

Abstract

Background: Methadone Maintenance Treatment is a useful method for opioid dependents, which results in harm reduction and increased quality of life in opioid dependents. The prevalence of psychiatric disorders in addicts is higher than in the general population which can interfere with the course and treatment of substance dependents and decrease the efficacy of treatment.

Methods: This descriptive, cross-sectional study was aimed to determine the correlation between psychiatric disorders and methadone dosage. It was performed on 154 patients of Kerman Shahid Beheshti Hospital's Methadone Clinic during a six month period from Dec 2010 to Jul 2011. The study population was chosen by convenience sampling. The searching tools were Socio-Demographic Questionnaire, psychiatric structured interview based on DSM-IV-TR, Beck Depression Inventory, Young Mania Rating Scales, and Anxiety and Depression Rating Scales.

Findings: Significant correlations were observed between increased methadone dosage and antisocial personality disorder. In addition, significant positive correlations were observed between increased methadone dosage and Hamilton anxiety scores, Hamilton depression scores and Young Mania scores.

Conclusion: High methadone dosage may be a marker of coexisting psychiatric disorders in patients on methadone maintenance treatment which indicates the necessity of devoting further attention to this group. Psychiatric services should be open and accessible to the patients, especially those who seek treatment voluntarily. Early diagnosis and treatment of patients with coexisting psychiatric disorders may increase the efficacy of methadone maintenance treatment.

Keywords: Methadone maintenance treatment, Psychiatric disorders, Substance dependents.

Addict & Health 2012; 4(1-2): 1-8

Received: 1.7.2011, Accepted: 4.10.2011

1- Assistant Professor, Child and Adolescent Psychiatrist, Neuroscience Research Center AND School of Medicine, Department of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran.

2- Resident, Department of Psychiatry, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

3- Iran Language Institute, Kerman, Iran.

4- Assistant Professor, Neuropsychiatrist, Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran.

Correspondence to: Arman Masoudi MD, Email: dr_arman58@yahoo.com

Introduction

Dependence on opoid is a chronic and mainly recurring disorder which causes many medical difficulties including AIDS and hepatitis as well as social problems. Due to its chronic feature, long-term and even sometimes permanent treatment is necessary through replacing opioids with substitutes such as methadone for alleviating physical and psychosocial hardships.¹⁻³

Methadone is a synthetic narcotic eaten orally that can substitute heroin. Methadone is given to the addicted patients instead of their administered drug and causes placation of withdrawal symptoms. Methadone maintenance is prescribed as far as it is possible to make the patient quit this drug, which is itself addictive, at later times. Methadone maintenance reduces death risk up to 70%, leads to a decrease in consumption of illegal narcotics and prevents from other drug abuse items, decreases crime rate, and finally lowers the risk of suffering from a variety of infectious diseases, most importantly AIDS and hepatitis B and C. It also causes 80% reduction in family fights and quarrels. The only demerit is that the patient might remain dependent on another narcotic drug.^{4,5}

People who abuse and suffer from dependence on narcotic drugs will also incur other disorders.⁴ Simultaneous reliance on several substances, depression and anxiety, and personality disarrangement are among the disorders associated with addiction.⁶ Mood disorders are the most prevailing kind of psychological suffering in heroin addicts and 12-24% of heroin-addicted people are simultaneously depressed.⁷ Overall, it can be stated that psychiatric disorders are more prevalent among addicted individuals than the public population.⁸ Diagnosis of these disorders plays a decisive role in medication and prognosis.⁹

Medication of drug abuse is less effective in the presence of psychiatric diseases and treatment becomes less efficient as the mental symptoms grow.¹⁰ Compared to the group of people who merely have addiction diagnosis, the addicted people simultaneously suffering from mental disorders require higher dosages of methadone and longer time of administration to reach a stable state. They proceed less successfully in the methadone

maintenance treatment and risk of withdrawal medication is high for them.¹¹ In the cases where the addicted patient does not accept to withdraw, measures must be taken so that the grounds are provided for lowering dangers caused by drug abuse.¹² In Iran, damage alleviation programs have been ratified and executed since 2001 in national and provincial scales; methadone maintenance treatment is one of the major services provided in such programs.¹³

Taking into account high costs of methadone maintenance programs, the chance of realizing objectives and interests of this plan would fail in the event of inconsistency of patients to follow the medication procedures. This study was conducted with the intent of determining the relationship between administered dosages of methadone and comorbid psychiatric disorders in volunteer patients admitted to the outpatient methadone clinic of Shahid Beheshti Psychiatric Hospital, Kerman, Iran. Having studied this relationship, the necessity for paying attention to psychiatric interventions in methadone-treated patients is further accentuated because by medicating the simultaneous psychiatric disorders, besides lowering the administered dosage of methadone which in turn reduces medication expenses, the methadone-induced complications will decrease and also the patients will become more consistent in the methadone maintenance treatment. Accordingly, objectives of the program are further realized bringing benefits to both the individual and the society.

Methods

The current study is a cross-sectional descriptive survey. The studied population comprised of 154 individuals selected through simple sampling method from all patients admitted to the methadone clinic of Shahid Beheshti Hospital, Kerman, within a 6-month period (February 2011-August 2011).

First the participation in the research was explained by clinic nurses to the people treated with methadone who refer to the clinic every day to receive methadone. Demographic details and administered methadone data forms were then recorded by the nurses based on patient files. Subsequently, a psychiatrist aide held clinical psychiatric interviews with all participants; the

interview was arranged in accordance with DSM-IV-TR standard. Finally, Back's depression questionnaire was completed by the patients themselves (self-report) and Hamilton's depression and anxiety scales and Young Mania Rating Scale were completed by the aide.

The patients' methadone dosage had been adjusted prior to entry into the program according to the methadone maintenance protocol of the Ministry of Health and Medical Education. Those patients who participated in the program had received a fixed dosage of methadone for at least two weeks. The interviewer had no knowledge of the administered dosage of methadone while doing the interview or completing the questionnaires. The data were statistically analyzed using SPSS software 17 and ANOVA and Spearman tests.

Results

Out of the 154 studied patients, 147 people were male (95.5%) and 7 were female (4.5%). Minimum and maximum methadone dosages in the studied individuals were 10 mg and 220 mg, respectively; average methadone dosage was 86.16 mg.

According to the clinical psychiatric interview structured based on DSM-IV-TR, 38 people (24.7%) had major depressive disorder (MDD), 7 (4.5%) suffered from bipolar mood disorder (BMD), 13 had anxiety disorders (including OCD, PANIC, PTSD), 9 people had record of ADHD in childhood (based on description of childhood times), 4 people suffered from adult ADHD, and 17 participants (11%) suffered from major depressive disorder and anxiety disorders simultaneously. Moreover, 22 individuals (14.3%) had anti-social personality disorder, 24 (15.6%) had borderline personality disorder and 7 people (4.5%) suffered from paranoid personality disorder.

As shown in table 1, the average administered dosage of methadone was 86.42 mg for those who had no disorder of "I" axis. This figure was 103.42, 75.71, 93.46, 71.76, and 82.35 (mg) respectively for the persons with MDD, BMD, anxiety disorders (including OCD, PANIC, and PTSD), childhood ADHD, adult ADHD, and finally, those simultaneously having major depressive disorder and anxiety disorders.

According to the statistical survey conducted by using analysis of variance and

observing the required preconditions, there is no significant statistical correlation between levels of suffering from psychiatric disorders of "I" axis and methadone dosage.

According to table 2, the average administered dosage of methadone was 81.73 mg in people who did not have personality disorder of "II" axis; this figure is respectively 110.68, 96.46, and 103.57 for those suffering from anti-social personality disorder, borderline personality disorder, and paranoid personality disorder.

Based on the statistical analysis, there is a statistically significant correlation between psychiatric disorders of "II" axis and administered dosage of methadone ($P = 0.005$). Results of post-hoc tests (TUKEY test) proved that the participants suffering from anti-social personality disorder require a significantly higher dosage of methadone compared to those who have no personality disorder; but such an impact was not observed in other personality disorders.

For the studied patients, maximum and minimum scores were 1 and 61 in Back's depression questionnaire and average score was 20.55. Minimum, maximum, and mean scores were respectively 0, 25 and 8.12 for Hamilton's depression scale. The same scores were 0, 21, and 5.6 for Hamilton's anxiety scale, respectively. In Young Mania Rating Scale, these figures were 0, 7, and 0.39 in the same order.

According to table 3:

There is no significant statistical correlation between Back's depression test scores in the studied individuals and methadone dosage ($P = 0.140$), and the relationship of two variables is not extendable.

There is a significant statistical relationship between Hamilton's depression test scores in the studied individuals and methadone dosage ($P = 0.010$), and scores of Hamilton's depression test and administered methadone dosage are positively correlated; i.e. administered dosage of methadone increases with higher scores of Hamilton's depression test scores.

There is a significant statistical relationship between Young Mania Rating Scale scores in the studied individuals and methadone dosage ($P = 0.010$), and scores of Young Mania Rating Scale and administered methadone dosage are positively correlated; i.e. administered dosage of methadone increases with higher scores of Young Mania Rating Scale scores.

Discussion

Based on the clinical interview in accordance with DSM-IV-TR in the current study, the most prevalent psychiatric disorders in the methadone-treated patients were major depressive disorder (24.7%), borderline personality disorder (15.6%), anti-social personality disorder (14.3%), and simultaneous anxiety disorders and major depressive disorder (11%).

Totally, 51.2% of methadone-treated patients suffered from psychiatric disorders of "I" axis and 34.4% of them had some sort of personality disorder with borderline personality disorder as the most prevailing item (15.6%). the latter result is not in agreement with Brooner et al.'s study, in which anti-social personality disorder is the most frequent case (33.9%).¹⁴ One of the reasons for different results of the present study might be due to the fact that the studied individuals have been selected from volunteers

admitted to an academic psychiatric center for methadone maintenance, and hence considering the higher probability of attendance of people with anti-social personality disorder in other places such as prisons, and the likelihood of their avoidance from being admitted to psychiatric centers, the aforementioned disorder in our statistical population is observed less frequently than the actual level. Moreover, people with borderline personality disorder are more in need of psychiatric medication due to lack of sensational and behavioral stability and are likely to refer more frequently to academic hospitals because of their acquaintance with such medical centers. Furthermore, this difference might result from exceeded abundance of borderline personality disorder compared to the past, which must be investigated in the society.

On the other hand, 34.4% of methadone-

Table 1. Correlation of methadone dosage and psychiatric disorders of "I" axis according to DSM-IV-TR (Diagnostic and statistical manual of mental disorders, 4th Edition, Text revision) in research samples

	Quantity	Average methadone dosage	Standard deviation	P-value
MDD	38	103.42	44.6	0.130
Anxiety Disorders	13	93.46	30.0	
BMD	7	75.71	42.6	
Childhood ADHD record	9	71.67	23.1	
Adult ADHD	4	70.00	43.0	
MDD + Anxiety D.	17	82.35	29.7	
Total studied patients	154	89.16	38.5	

MDD: Major depressive disorder; BMD: Bipolar mood disorder; ADHD: Attention deficit hyperactivity disorder

Table 2. Correlation of methadone dosage and psychiatric disorders of "II" axis according to DSM-IV-TR (Diagnostic and statistical manual of mental disorders, 4th Edition, Text revision) in research samples

	Quantity	Average methadone dosage	Standard deviation	P-value
Without certain diagnostic disorder	101	81.73	34.8	0.005
Anti-social personality disorder	22	110.68	43.3	
Borderline personality disorder	24	96.46	39.2	
Paranoid personality disorder	7	103.57	45.1	
Total studied patients	154	89.16	38.5	

Table 3. Correlation of methadone dosage and scores of Beck, Hamilton's Depression, Hamilton's Anxiety, and Young Mania Rating Scales disorder tests

Methadone Dosage		
	Rho (Spearman)	P-value
Beck's depression test	0.119	0.140
Hamilton's depression test	0.207	0.010
Hamilton's Anxiety Scale	0.182	0.024
Young Mania Rating Scale	0.172	0.034

treated individuals suffered from one personality disorder, which is relatively in alignment with the findings of the research by Brooner et al. where 40.5% of addicts had personality disorders.¹⁴

According to results of the current study, suffering from a psychiatric disorder of "I" axis did not have a significant impact on the administered dosage of medicine for methadone-treated patients. In Maremmi et al.'s studies, however, people showing symptoms of somatization, depression and anxiety and also bipolar disorder required higher dosages of methadone.¹⁵ Moreover, in a study by Eslami et al. conducted similar to the current research based on psychiatric disorder diagnosis of "I" and "II" axes through DSM-IV-TR interview, depression, anxiety and bipolar disorders were accompanied with an increase in initial methadone dosage.¹⁶

There was a statistically significant correlation between psychiatric disorders of "II" axis and administered dosage of medicine in methadone-treated patients. Results of post-hoc tests (TUKEY test) proved that the people suffering from anti-social personality disorder significantly need higher dosage of methadone compared to those who have no personality disorders; but such an impact was not observed in other personality disorders. This result is not in agreement with the findings of studies by Murray et al., Treece and Nicholson, Maremmi et al., and Eslami et al. who inferred that the patients suffering from schizoid and paranoid personality disorders and anti-social and borderline disorders need higher methadone dosages.¹⁵⁻¹⁹

There was no statistically significant correlation between scores of Back's depression test and administered dosage of medicine in methadone-treated individuals. This lack of correlation seems to result from the improper collaboration of some patients in completing Back depression questionnaire in self-report form, and in some cases this drawback is caused by careless and completion without reading of questionnaires. In addition, the bias observed in the results might be related to excessive depiction of symptoms in the Back's questionnaire by some patients; this could originate from drug abuse and/or receiving methadone overdose.

There was a significant statistical correlation between administered methadone dosage and

scores of Hamilton's depression test, where methadone dosage increased with a higher score of Hamilton's depression test. This result is in accordance with findings of the study by Peles et al. in which score of Hamilton's depression test is positively correlated to methadone dosage.²⁰

Furthermore, a significant statistical correlation was also observed between administered methadone dosage and scores of Hamilton's anxiety test, where methadone dosage increased with a high score of Hamilton's anxiety test.

There also exists a significant statistical correlation between administered methadone dosage and scores of Young Mania Rating Scale, and methadone dosage increases with the ascending score of Young Mania Rating Scale.

Results of the current research and other studies are indicative of psychiatric disorders of "I" and "II" axes in methadone-treated patients. The evidence suggest that although simultaneous presence of "I" axis psychiatric disorders had no correlation with the increase in administered methadone dosage; there was a positive correlation between medicine dosage and intensity of anxiety, depression, and mania symptoms. Exceeded intensity of symptoms led to an increment in methadone dosage. Besides, the addicted patients with simultaneous psychiatric disorders are less consistent in following the treatment procedures. They are highly prone to quitting the treatment and need higher dosages and a longer time for stabilization.²¹

Therefore, high methadone dosage might serve as a marker for the simultaneous presence of other psychiatric disorders in methadone-treated patients. This implies the necessity for further investigation of patients who need higher dosages of methadone for comorbidity because diagnosis and medication of simultaneous disorders in such patients would result in the reduction of administered methadone dosage, alleviation of methadone complications (adverse side effects), and ultimately, decrease in financial costs. More importantly, these benefits will improve the consistency of patients in methadone treatment leading to the further realization of the objectives of the current research.

Recommendations

Taking into account the above discussions,

availability of psychiatric services for patients, especially for those voluntarily seeking help and medication, coupled with timely diagnosis and treatment of individuals suffering from simultaneous psychiatric disorders will apparently contribute to the improvement of benefits of methadone maintenance treatment and further realization of the current research objectives.

Future studies are recommended to investigate the medical interventions and also to evaluate the variations in administered methadone dosage following the treatment.

Limitations

Abuse of drugs by patients and withdrawal

References

1. Asaadi SH. Two important problem in 21th century: population growth and drugs. Tehran, Iran: Sepehr Publishing; 1997. [In Persian].
2. The Ministry of Health and Medical Education of Iran. Practical Guide of Treatment of Substance Abusers. 2nd ed. Tehran, Iran: Ministry of Health and Medical Education; 2002. [In Persian]
3. Mostashari G. Preliminary guideline in methadone maintenance therapy. Tehran: Department of Prevention and Treatment Addiction, Ministry of Health and Medical Education; 2002. Available from: URL: <http://www.sapto.hbi.ir/PDF/mmprimpl.pdf>.
4. Kaplan HI, Sadock BJ. Synopsis of Psychiatry: Behavioral Sciences, Clinical Psychiatry (Kaplan Sadock psychiatry). 10th ed. New York, NY: Lippincott Williams and Wilkins; 2007.
5. Parvaresh N, Kheradmand A, Darijani M. The Effect of Methadone Maintenance Therapy on Harm Reduction in Opiate Dependents in Kerman Socio-Behavioral Consulting Centers. *Journal of Addiction and Health* 2010; 2(1-2): 26-9.
6. Shudofsky M. Excerpts from the book War and the Globalization of Opium and Heroin: Mass production of the most deadly weapons in Afghanistan. Trans: Pouya J. 2nd ed. Tehran, Iran: The Secretariat of Drug Control Headquarters; 2004. [In Persian].
7. Wieland WF, Sola S. Depression in opiate addicts measured by objective tests. *Proceedings of the 3rd National Conference on Methadone Treatment*; 1970 Nov 16; New York, NY.
8. Heidari Pahlavian A, Amirzargar M, Farhadinasab A, Mahjub H. Comparing Personality Characteristics of Addicts with Non Addicts in Hamadan. *Sci J Hamdan Univ Med* 2003; 10(2): 55-62.
9. Maremmanni I, Pacini M, Popovic D, Romano A, Maremmanni AG, Perugi G, et al. Affective temperaments in heroin addiction. *J Affect Disord* 2009; 117(3): 186-92.
10. McLellan AT, Luborsky L, Woody GE, O'Brien CP, Druley KA. Predicting response to alcohol and drug abuse treatments. Role of psychiatric severity. *Arch Gen Psychiatry* 1983; 40(6): 620-5.
11. Maremmanni I, Perugi G, Pacini M, Akiskal HS. Toward a unitary perspective on the bipolar spectrum and substance abuse: opiate addiction as a paradigm. *J Affect Disord* 2006; 93(1-3): 1-12.
12. Bagheri Yazdi A, Shams Alizadeh N, Abedin A, Mostashari G, Vazirian M. The Guide to the Prevention and Treatment of Substance Abuse. Tehran, Iran: Salman Publications; 2006. [In Persian].
13. Naderi N, Binazadeh M, Sefatian S, Asghar Peyvandi A. Comprehensive text book of addiction: Dependence to different substances and their pharmacological and non-pharmacological treatment. 2nd ed. Tehran, Iran: Drug Control Headquarters; 2009. [In Persian].
14. Brooner RK, King VL, Kidorf M, Schmidt CW, Jr., Bigelow GE. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch Gen Psychiatry* 1997; 54(1): 71-80.
15. Maremmanni I, Zolesi O, Agueci T, Castrogiovanni P. Methadone doses and psychopathological symptoms during methadone maintenance. *J Psychoactive Drugs* 1993; 25(3): 253-6.
16. Eslami Shahrabaki M, Ziaaddini H, Hagh Doost AA, Ghasemi M, Eslami Shahrabaki P, Alizadeh Nouri R, et al. Methadone Treatment in Iranian Opiate Addicts: A Preliminary Report.

symptoms could cause bias in the clinical assessment and also findings of the questionnaire and might lead to mistaken diagnosis of anxiety and depression disorders. It is recommended that patients be analyzed in terms of abuse of drug and narcotic in the future studies.

Conflict of Interest: The Authors have no conflict of interest.

Acknowledgement

We must deeply express our thanks to endeavors of Shahid Beheshti Hospital - Methadone Clinic's personnel for data collection, and also to the financial and spiritual supports of Kerman Neurosciences Research Center that helped us accomplish this research.

- Addiction and Health 2011; 3(1-2): 53-60.
17. Ross HE, Glaser FB, Germanson T. The prevalence of psychiatric disorders in patients with alcohol and other drug problems. *Arch Gen Psychiatry* 1988; 45(11): 1023-31.
 18. Murray H, McHugh RK, Behar E, Pratt E, Otto M. Personality factors associated with methadone maintenance dose. *Am J Drug Alcohol Abuse* 2008; 34(5): 634-41.
 19. Treece C, Nicholson B. DSM-III personality type and dose levels in methadone maintenance patients. *J Nerv Ment Dis* 1980; 168(10): 621-8.
 20. Peles E, Schreiber S, Naumovsky Y, Adelson M. Depression in methadone maintenance treatment patients: rate and risk factors. *J Affect Disord* 2007; 99(1-3): 213-20.
 21. Maremmani I, Canoniero S, Pacini M. Methadone dose and retention in treatment of heroin addicts with Bipolar I Disorder comorbidity. Preliminary Results. *Heroin Addiction and Related Clinical Problems* 2000; 2(1): 39-46.

بررسی ارتباط بین دوز مصرفی متادون با اختلالات روان‌پزشکی همراه در بیماران تحت درمان نگهدارنده با متادون

دکتر نوشین پرورش^۱، دکتر آرمان مسعودی^۲، شیوا مجیدی تبریزی^۳، دکتر شهرزاد مظهري^۴

چکیده

مقدمه: درمان نگهدارنده با متادون از جمله روش‌های درمانی مفید در افراد وابسته به مواد افیونی است که سبب کاهش آسیب و افزایش کیفیت زندگی این افراد می‌شود. شیوع اختلالات روان‌پزشکی در معتادان بسیار بیش‌تر از جمعیت عمومی می‌باشد که می‌تواند در سیر درمان افراد وابسته به مواد تداخل ایجاد کرده و سبب کاهش کارایی درمان شود.

روش‌ها: مطالعه مقطعی- توصیفی حاضر با هدف، تعیین ارتباط بین دوز مصرفی متادون با اختلالات روان‌پزشکی همراه بر روی ۱۵۴ مراجعه‌کننده به کلینیک متادون بیمارستان شهید بهشتی کرمان در سال ۹۰-۱۳۸۹ و در یک دوره ۶ ماهه انجام شد. ابزارهای پژوهش شامل مصاحبه ساختار یافته روان‌پزشکی بر اساس DSM IV-TR، پرسش‌نامه جمعیت‌شناختی، پرسش‌نامه افسردگی Beck، مقیاس‌های Young Mania و پرسش‌نامه اضطراب و افسردگی Hamilton بود.

یافته‌ها: اختلال شخصیت ضد اجتماعی با افزایش دوز متادون مصرفی ارتباط معنی‌داری داشت ($P < 0/01$). همچنین بین نمرات مقیاس‌های افسردگی و اضطراب Hamilton، مقیاس Young Mania و افزایش دوز متادون مصرفی ارتباط معنی‌داری مشاهده شد ($P < 0/05$).

نتیجه‌گیری: در بیماران تحت درمان نگهدارنده با متادون، ممکن است دوز بالای متادون نشانه وجود اختلالات روان‌پزشکی همزمان بوده و بیانگر لزوم توجه بیش‌تر به این گروه می‌باشد. بنابراین، در دسترس بودن خدمات روان‌پزشکی برای بیماران، به ویژه آن‌هایی که داوطلبانه به دنبال درمان هستند و همچنین تشخیص و درمان به موقع افراد مبتلا به اختلالات روان‌پزشکی، همزمان موجب افزایش کارایی درمان نگهدارنده با متادون می‌شود.

واژگان کلیدی: درمان نگهدارنده با متادون، اختلالات روان‌پزشکی، وابستگی به مواد.

مجله اعتیاد و سلامت، سال چهارم، شماره ۲-۱، زمستان و بهار ۹۱-۱۳۹۰

تاریخ پذیرش: ۹۰/۷/۱۲

تاریخ دریافت: ۹۰/۴/۱۰

۱- استادیار، روان‌پزشک کودک و نوجوان، مرکز تحقیقات علوم اعصاب و دانشکده پزشکی، گروه روان‌پزشکی، دانشگاه علوم پزشکی کرمان، کرمان، ایران.

۲- دستیار، گروه روان‌پزشکی، دانشکده پزشکی، دانشگاه علوم پزشکی کرمان، کرمان، ایران.

۳- کانون زبان ایران، کرمان، ایران.

۴- استادیار، روان‌پزشک، دکترای تخصصی نوروسایکیاتری، مرکز تحقیقات علوم اعصاب، دانشگاه علوم پزشکی کرمان، کرمان، ایران.